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U.S. High Production Volume (HPV) Chemical Challenge Program

CATEGORY DEVELOPMENT AND JUSTIFICATION, AND PROPOSED TEST PLAN FOR ALUMINUM STEARATES

The Metal Carboxylates Coalition

A SOCMA Affiliated Consortium

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SUMMARY

The Metal Carboxylates Coalition has sponsored 20 compounds that are metal salts of carboxylic acids. Metal Carboxylates are metal salts of carboxylic acids. These compounds readily dissociate to the corresponding metal and carboxylic acid. The HPV endpoints are fulfilled using a combination of data from the parent molecule, as well as for the dissociation products; that is, a metal salt and/or a carboxylic acid. Selected testing of the parent molecules has been proposed to further fulfill HPV endpoints. Robust summaries are provided for the parent molecules as well as the dissociation products.

This submittal provides the information for:

Aluminum Distearate	300-92-5
Aluminum Tristrearate	637-12-7

The proposed testing is presented in the attached Test Plan matrix (Table 3)

1.0 BACKGROUND

This submittal provides the information for:

Aluminum Distearate	300-92-5
Aluminum Tristrearate	637-12-7

Figure 1 provides structures of these two related materials.

1.1 Use Patterns for Metal Carboxylates

The metal carboxylates function to deliver a metal ion into chemical reactions. The carboxylic acids (acids) are tailored for use in different products or chemical reactions.

1.2 Common Characteristics of Metal Carboxylates

These two metal carboxylates (aluminum di- and tri-stearate) are functionally similar and have the same ionizable substituents, the same metal cation, and a structurally similar carboxylic acid group (RCOOH). These compounds are divalent compounds and have two carboxylic acid moieties per molecule. The metal carboxylate salts are designed to add metals to chemical reactions; therefore, they are designed to readily dissociate into the free metal and free acid.

2.0 Dissociation Studies

One key characteristic of metal carboxylates is that they readily dissociate from an ion pair into free metal and free acid. They are found as partially dissociated products in the ambient environment (i.e., neutral pH). Dissociation is a reversible process and the portion of dissociated salt present is dependent on the pH and pKa (the dissociation constant), which is the pH at which 50% dissociation occurs. In the low pH environment of the digestive tract (e.g., pH 1.2) complete dissociation will occur for these metal carboxylates. The transport and bioavailability of the metals and acids are determined by their solubility in environmental media and biological fluids which is determined by environmental parameters such as pH.

Completion of the dissociation study with these two aluminum stearate compounds was not possible due to low water solubility, although these compounds are expected to readily dissociate (Crompton Corporation, personal communication). Studies with other metal carboxylates indicate that significant dissociation will occur at approximately neutral pH (i.e., representative of aquatic and marine ecosystems), while complete dissociation will occur at physiologically relevant pH of the mammalian stomach (pH 1.2). These findings are particularly important in relating available data for the respective acids and metals to support

the existing data for aluminum di- and tri-stearate and in the fulfillment of critical endpoints.

Dissociation is a reversible reaction, splitting the parent compound into two or more chemical species which may be ionic, but are not necessarily so. The process can be generally represented as:

High pH		Low pH
$[RCOO^-]_x:[M^+]_x$	$[RCOO^-]_x + [M^+]_x$	$[RCOOH]_x + [MCl]_x$
(salt)	(Titrate with HCl)	free acid and free metal

The pKa and pH are equal when the metal carboxylate salt is 50% dissociated. The parent compounds, the metal carboxylate salts, are associated ionized molecules.

The dissociation constant is important for two reasons. First, it determines the proportion of any specific acid or metal that is dissociated at a given pH. The free acid and corresponding free metal are often much different than the salt (ion pair) moiety in characteristics such as solubility, adsorption, and toxicity. The proportion of dissociation influences the behavior of the substance in the environment and bioavailability of the acid and metal constituents of metal carboxylate salts.

The dissociation constants for 18 related metal carboxylate compounds tested have pKa (pKb) values (pKa1) in the neutral range (5.088 to 8.448). This indicates that in the neutral pH range, significant portions of the metal carboxylates will be dissociated. In addition, at the low pH of the mammalian stomach (pH 1.2) all of the metal carboxylates would be expected to be completely or nearly completely dissociated. This indicates that the absorption and any observed toxicity would be independent for the respective acid and metal when administered orally. The aluminum stearate compounds are expected to behave similarly.

The dissociation constants show that at the pH of the stomach and at the pH of environmental media the important moieties are the ionized free acid and metal. Because of this, environmental fate, ecotoxicity, and mammalian toxicity of the free acid, or that for a simple salt (e.g., the sodium salt), can to serve as a surrogate data for the acid component of respective metal carboxylates. Similarly, under these conditions, data for the metal ion can be represented by fate and toxicity data on of free metal ion or simple metal salts (e.g., metal chlorides). Therefore, the role in any observed toxicity for acids and metals can be evaluated independently (i.e., as the free metal and/or free acid).

3.0 Bioequivalency

The work described below by Stopford et al. (unpublished)[1] shows that the metal chloride is similar to, or more bioavailable than, the corresponding metal carboxylate salts, which makes the chloride a conservative surrogate in estimating bioavailability and toxicity of dissociated metals. Chlorides of the various metals have been emphasized during preparation of the attached robust summaries and are the preferred surrogate data for carboxylate salts.

Recent studies conducted to evaluate the "bioequivalency" (an estimate of bioavailability) of cobalt compounds, included three cobalt carboxylates and cobalt chloride. The solubility of these compounds in synthetic biological fluids (gastric juices, intestinal juices, several interstitial fluids, and cytosol) showed that these salts were completely dissociated and dissolved at gastric pH and cytosolic pH. The dissolution of these compounds ranged from 26.1% to 80.4 % of available cobalt at neutral pH (Table 1). The results for cobalt chloride and cobalt 2-ethyl-hexanoate were very similar at acidic and neutral pH. Cobalt neodecanoate and cobalt naphthenate showed similar levels of dissolution at acidic (gastric and cytosolic) pH, but smaller proportions of the metal component of these compounds were dissolved at neutral pH. The differences in dissolution for these metal carboxylates at neutral pH in synthetic body fluids could be related to differences in their dissociation constants.

These data are valuable in understanding the aluminum stearates for three reasons:

1. They confirm the prediction that these stearate compounds would be expected to be completely dissociated in the gastrointestinal tract (low pH) and a substantial proportion of these compounds would be expected to be dissociated and bioavailable at neutral pH (7.4).

2. The fraction of the three cobalt carboxylates that is dissolved at acidic and neutral pH is very similar for different acid constituents with a range of molecular weights and chain lengths. This finding greatly strengthens the extrapolation of the results to the aluminum stearates.

3. The work by Stopford et al. (unpublished) shows that the metal chloride is similar to, or more bioavailable than, the corresponding metal carboxylate salts, which makes the chloride a conservative surrogate in estimating

[1] Stopford, W., J. Turner, D. Cappellini, and T. Brock. (unpublished) Bioequivalency Testing of Cobalt Compounds (Oct 15, 2002 Draft). Conducted by Duke University Medical Center, Division of Occupational and Environmental Medicine for the Cobalt Development Institute, Research Triangle Park, N.C.

bioavailability and toxicity of dissociated metals. Chlorides of the various metals have been emphasized during preparation of the attached robust summaries and are the preferred surrogate data for carboxylate salts.

4.0 Supporting Data for Aluminum Stearates and their Dissociation Products

Data for the aluminum stearates (Appendix C and D) and their dissociation products (aluminum chloride and Stearic acid, Appendix A and B, respectively) are provided in robust summary format.

Consistent with discussions between the Metal Carboxylates Coalition and the EPA, data for the dissociation products (metals and acids) are recognized as being essential to understanding the environmental fate and toxicological characteristics of the respective metal carboxylate salts. Data for stearic acid and aluminum are useful in characterizing the hazard of the aluminum stearate compounds.

In summary, the key points relative to the two aluminum stearates are:

- Dissociation to stearic acid and aluminum (described as aluminum chloride);
- Expected Dissociation constants (pKa) in the circum neutral range (5.088 to 8.448);
    - Complete or nearly complete dissociation at gastric and cytosolic pH levels;
    - A moderate to high proportion of dissociation in the neutral pH range;
- General bioequivalency for salts with the same metal cation (cobalt used as an example within this document) and different acids or the chloride salt;
- Aluminum stearates have the same use pattern, to provide free metal ion to chemical reactions.
- Provision of data for the parent molecule or one or both of its dissociation products

5.0 Proposed Test Plan

The aluminum stearates are the high molecular weight compounds (~610 for aluminum distearate and ~877 for aluminum tristearate). The Metal Carboxylates Coalition has relied on the fact that these compounds will dissociate and that the respective acid (stearic acid), and metal (aluminum) are the chemicals of interest. Although dissociation was not demonstrated as these materials have water solubility's too low to allow analysis by the standard

methods (OECD Guideline 112), these two compounds are expected to dissociate readily in water at neutral pH's and to be completely dissociated at the pH of the stomach (pH 1.2) as demonstrated for other metal carboxylates.

Stearic acid has a long history of safe use in foods and cosmetics. This compound is sponsored by the Aliphatic Acids Category under the HPV Challenge Program.

The Metal Carboxylates Coalition is relying on the data for stearic acid and aluminum to support these two materials and to minimize unnecessary testing. The Coalition has prepared an interim robust summary document for stearic acid which describes the necessary endpoint data under the HPV Program (Appendic A). More complete or more robust data may become available following submission of the Aliphatic Acids Category submission is made to the EPA under the HPV Challenge Program by the Soap and Detergents Association. If needed, the Metal Carboxylates Coalition will then revise the current robust summaries document to include the complete stearic acid data and will make a supplemental submission. The stearic acid salts will not be tested for these data elements, because stearic acid is a surrogate for the stearic acid salts based on known dissociation at neutral pH and at gastric pH. A robust summary document has also been prepared for aluminum chloride (Appendix B).

Physicochemical Properties:

Table 2 provides a summary of the available physical chemical data for the aluminum stearates, as well as their dissociation products. Melting point data are available for both materials. Both are expected to decompose such that a boiling point test is not necessary. Vapor pressure are anticipated to be very low (modeling data indicate vapor pressures will be in the range of 4E-17 mm Hg (distearate) to 1.08E-18 mm Hg (tristearate). The water solubility of these materials is very low (nearly insoluble).

No additional physical chemical properties testing is necessary or proposed.

Environmental Fate:

Table 2 provides a summary of the available environmental fate data for the aluminum stearates, as well as their dissociation products. Most test of environmental fate (partition coefficient, stability on water and biodegradation) are not appropriate for these materials due to their very low water solubility. Model estimates of these parameters are presented in Table 2. Partition coefficient and biodegradation studies are available for stearic acid, which is considered to be representative of the two materials since these compounds dissociate and stearic acid will be the moiety of interest. Stearic acid is readily biodegradable, and has a partition coefficient of >8. Photodegradation and

transport (fugacity) have been calculated using SAR models (e.g., EPIWIN) for the aluminum stearates.

No additional environmental fate properties testing is necessary or proposed.

Environmental Effects:

Table 2 provides a summary of the available environmental effects data for the aluminum stearates, as well as their dissociation products. Due to the very low water solubility of these materials, as well as the low water solubility of stearic acid, acute aquatic toxicity tests are not expected to be relevant.
A daphnia reproduction study with aluminum distearate is proposed for aquatic toxicity testing.

Human Health Effects:

Data elements for human health effects endpoints were examined for the aluminum stearates, stearic acid and aluminum (Table 2). Mammalian toxicity will be represented by data available for the dissociation products. The Coalition will also rely on the results of the Aliphatic Acids Consortium submission to address other data elements for stearic acid. When they become available, these data will be incorporated this Test Plan.

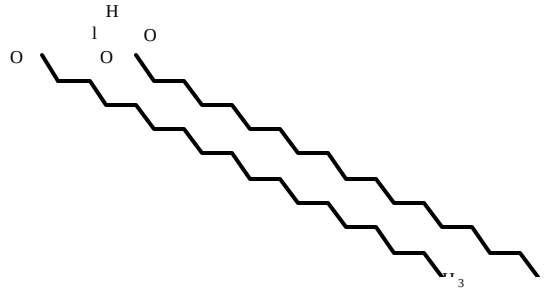
A 7 day repeat dose toxicity study with aluminum distearate is proposed as a bridging study to show that dissociation product data is representative of the aluminum stearates toxicity.

5.1 TEST PLAN SUMMARY

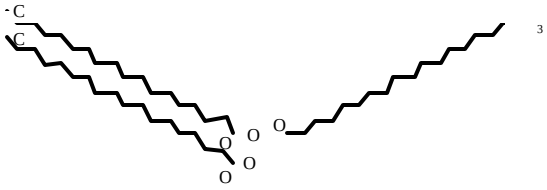
Table 3 provides the test plan for the two aluminum stearate materials. A daphnia reproduction test and a 7-day repeat dose toxicity test are proposed with aluminum distearate.

FIGURES

Figure 1: Structures



MolWt: 610.95 C36 H71 O5 Al1
000300-92-5 Aluminum, hydroxybis(octadecanoato-O)-



MolWt: 877.42 C54 H105 O6 Al1
000637-12-7 Aluminum stearate

TABLES

Table 1: Results of Extraction of Cobalt from Surrogate Biological Fluids

Matrix (pH)	**Maximum Solubility (% of available metal)**			
	$CoCl_2$	Co 2-ethyl-hexanoate	Co naphthenate	Co neodecanoate
Gastric pH (1.5)	>91.6	100	>85.7	100
Intestinal pH (7.4)	>79.4	50.8*	45.4*	30.8*
Alveolar pH (7.4)	>68	>59.6	35.4*	26.1*
Interstitial pH (7.4)	78.4	>80.4	40*	43.1*
Serum	>85	>66.9	42.9*	46.6*
Intracellular pH (4.5)	>89.6	100	>79.1	>78.1

* maximum extraction level at 72 hours

All data is taken from Stopford et al. (unpublished) Bioequivalency Testing of Cobalt Compounds. Conducted by Duke University Medical Center, Division of Occupational and Environmental Medicine for the Cobalt Development Institute.

Table 2: Summary of Available and Relevant Data for Aluminum Stearates and Dissociation Products

Compound	**Physical Chemical Properties**			
	Melting Point (deg C)	Boiling Point (deg C)	Vapor Pressure (hPa)	Water Solubility (g/L)
Aluminum Distearate	145	-	-	Not water soluble
Aluminum Tristearate	100-120	Decomposes	-	Not water soluble
Dissociation Product: Aluminum chloride	190	182	1.38 @ 100 deg C	450 @ 20 deg C
Dissociation Product: Stearic acid	69-70	383	1.33 @174	.00568 @25 deg C

Table 2 (continued): Summary of Available and Relevant Data for Aluminum Stearates and Dissociation Products

Compound	**Environmental Fate**				
	Partition Coefficient	Stability in Water	Photodegradation	Level III Fugacity Model	Biodegradation
Aluminum Distearate	- (not soluble in water)	- (not soluble in water)	.248 days	Air: 0.126 Water: 3.35 Soil: 30 Sediment: 66.5	- (not soluble in water)
Aluminum Tristearate	- (not soluble in water)	- (not soluble in water)	.2 days	Air 0.0598 Water 2.35 Soil 29.9 Sediment 67.7	- (not soluble in water)
Dissociation Product: Aluminum chloride	1.26 (calc)	Unstable	-	Air: 5.39E-006 Water: 39.8 Soil: 60.1 Sediment: 0.0767	-
Dissociation Product: Stearic acid	8.42	- (low water solubility)	T ½= .5 days	Air: 0.676 Water: 7.19 Soil: 28.9 Sediment: 63.3	Readily biodegradable

Table 2 (continued): Summary of Available and Relevant Data for Aluminum Stearates and Dissociation Products

Compound	**Environmental Effects**			
	Acute Toxicity to Fish (mg/L)	Acute Toxicity to Daphnia (mg/L)	Acute Toxicity to Algae (mg/L)	Chronic Toxicity to Daphnia (mg/L)
Aluminum Distearate	- (not soluble in water)	- (not soluble in water)	- (not soluble in water)	-
Aluminum Tristearate	- (not soluble in water)	- (not soluble in water)	- (not soluble in water)	-
Dissociation Product: Aluminum chloride	96 hr LC50 = 8.6	48 hr EC50=1.5	-	-
Dissociation Product: Stearic acid	96 hr = 12	-	-	-

Table 2(continued): Summary of Available and Relevant Data for Aluminum Stearates and Dissociation Products

Compound	**Mammalian Toxicity**				
	Acute Toxicity (mg/kg)	Repeat Dose Toxicity	Reproductive Effects	Developmental Effects	Genetic Toxicity
Aluminum Distearate	-	-	-	-	-
Aluminum Tristearate	-	-	-	-	-
Aluminum chloride	LD50 = 370 (rat)	NOAEL (mouse) = 195 (5 or 7 weeks)	NOAEL (3-gerneration reproductive study in mice) = 19.3 mg/kg/d	NOAEL (fetal toxicity; rat) = 75 mg/kg LOAEL (maternal toxicity; rat) = 75 mg/kg	Bacterial mutation =negative Mammalian cell mutation (in vitro or in vivo) = negative
Stearic acid	LD50 = 4600 (rat)	50 g/kg/d for 24 weeks produced reversible lipogranulomas	-	-	-

Table 3: Test Plan for Aluminum Stearates

Compound	Physical Chemical Properties			
	Melting Point (deg C)	Boiling Point (deg C)	Vapor Pressure (hPa)	Water Solubility (g/L)
Aluminum Distearate	A	NA	NA	NWS
Aluminum Tristearate	A	NA	NA	NWS

Table 3 (continued): Test Plan for Aluminum Stearates

Compound	Environmental Fate				
	Partition Coefficient	Stability in Water	Photodegradation	Level III Fugacity Model	Biodegradation
Aluminum Distearate	NWS	NWS	A	A	NWS
Aluminum Tristearate	NWS	NWS	A	A	NWS

Table 3 (continued): Test Plan for Aluminum Stearates

Compound	Environmental Effects			
	Acute Toxicity to Fish (mg/L)	Acute Toxicity to Daphnia (mg/L)	Acute Toxicity to Algae (mg/L)	Chronic Toxicity to Daphnia (mg/L)
Aluminum Distearate	NWS	NWS	NWS	Test
Aluminum Tristearate	NWS	NWS	NWS	R

Table 3(continued): Test Plan for Aluminum Stearates

Compound	**Mammalian Toxicity**				
	Acute Toxicity (mg/kg)	Repeat Dose Toxicity	Reproductive Effects	Developmental Effects	Genetic Toxicity
Aluminum Distearate	O/DP	O/DP	DP	DP	DP
Aluminum Tristearate	O/DP	O/DP	DP	DP	DP

A= Endpoint requirement fulfilled with adequate existing data
NA=Not applicable due to chemical/physical properties of the substance
NWS=Not applicable (not soluble in water)
R= Endpoint requirements to be fulfilled using data for aluminum distearate
Test= Endpoint requirements to be fulfilled with testing
DP= Endpoint requirements to be fulfilled using data for dissociation products
O/DP= Endpoint requirements to be fulfilled using data for dissociation products as well as a 7 day repeat dose bridging study with aluminum distearate